REMARKS

Provisional Rejection of Claims 1-20 Under the Judicially Created Doctrine of Obviousness-type Double Patenting

The Examiner has provisionally rejected Claims 1-20 under the judicially created doctrine of obviousness-type double patenting over Claims 1, 7-16 and 21 of USSN 10/757,981 (the "981 Application"); Claims 83, 98, 113, 128, 142 and 156 of USSN 10/846,978 (the "978 Application"); Claims 64-76 of USSN 11/119,357 (the "357 Application"); and Claims 1-20 of USSN 11/441,905 (the "905 Application").

Analysis of Claims 1, 7-16 and 21 of U.S. Serial No. 10/757,981

An obviousness-type double patenting rejection can be overcome by showing that the claims in question are patentably distinct. Claims 1-20 of the present invention are directed to a method of treating a functional bowel disorder, including diarrhea-predominant irritable bowel syndrome, in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a compound of Formula I and Formula II.

Claims 1, 7-16 and 21 of the '981 Application are directed to a method of treating nausea, vomiting, retching or any combination thereof in a subject in need thereof, wherein the nausea, vomiting, retching or any combination thereof is caused by an anesthetic, radiation, a cancer chemotherapeutic agent, a toxic agent, an odor, a medicine, pregnancy, motion, a condition which is associated with vertigo, headache or malady of the gastrointestinal (GI) tract, comprising administering to said subject a therapeutically effective amount of a compound of Formula I and Formula II. The therapeutic indications of the '981 Application and the present application are not the same. The claims of the '981 Application are directed to treating nausea, vomiting and retching that is caused by certain factors. In contrast, the claims of the present Application are directed to treating a functional bowel disorder. Thus, Claims 1-20 of the present invention and Claims 1, 7-16 and 21 of the '981 Application are patentably distinct.

Reconsideration and withdrawal of the rejection are respectfully requested.

Analysis of Claims 83, 98, 113, 128, 142 and 156 of U.S. Serial No. 10/846,978

As discussed above, Claims 1-20 of the present invention are directed to a method of treating a functional bowel disorder, including diarrhea-predominant irritable bowel syndrome in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a compound of Formula I and Formula II.

Claims 83, 98, 113, 128, 142 and 156 of the '978 Application are directed to a method of treating nausea, vomiting, retching or any combination thereof comprising administering about 0.001 mg to about 1000 mg per day of a compound of Formula II. The therapeutic indications of the '978 Application and the present application are not the same. The claims of the '978 Application are directed to treating nausea, vomiting, retching with a specific dose of Formula II. In contrast, the claims of the present Application are directed to treating a functional bowel disorder. Thus, Claims 1-20 of the present invention and Claims 83, 98, 113, 128, 142 and 156 of the '978 Application are patentably distinct.

Reconsideration and withdrawal of the rejection are respectfully requested.

Analysis of Claims 64-76 of U.S. Serial No. 11/119,357

As discussed above, Claims 1-20 of the present invention are directed to a method of treating a functional bowel disorder, including diarrhea-predominant irritable bowel syndrome, in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a compound of Formula I and Formula II.

Claims 64-76, including Claim 63, of the '357 Application are directed to a method of decreasing intestinal motility in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a compound of Formula I and Formula II. The therapeutic indications of the '357 Application and the present application are not the same. The claims of the '357 Application is directed to decreasing intestinal motility. In contrast, the claims of the present Application are directed to treating a functional bowel disorder. Thus, Claims 1-20 of the present invention and Claims 64-76 of the '357 Application are patentably distinct.

Reconsideration and withdrawal of the rejection are respectfully requested.

Analysis of Claims 1-20 of U.S. Serial No. 11/441,905

As discussed above, Claims 1-20 of the present invention are directed to a method of treating a functional bowel disorder, including diarrhea-predominant irritable bowel syndrome, in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a compound of Formula I and Formula II.

Claims 1-20 of the '905 Application are directed to a method of treating at least one symptom of irritable bowel syndrome selected from the group consisting of: abnormal stool frequency, abnormal stool form, abnormal stool passage, passage of mucus and feeling of abdominal distension in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a compound of Formula I and Formula II. The therapeutic indications of the '905 Application and the present application are not the same. The claims of the '905 Application are directed to treating specific symptoms of irritable bowel syndrome. In contrast the claims of the present Application is directed to treating a functional bowel disorder. Thus, Claims 1-20 of the present invention and Claims 1-20 of the '905 Application are patentably distinct.

Reconsideration and withdrawal of the rejection are respectfully requested.

Provisional Rejection of Claims 1-20 Under 35 U.S.C. § 101

The Examiner has provisionally rejected Claims 1-20 under 35 U.S.C. § 101 as claiming the same invention as that of Claims 1-20 of USSN 10/838,789; Claims 1-20 of USSN 10/841,317; Claims 1-20 of USSN 10/841,318; and Claims 1-20 of USSN 10/866,593.

Analysis of Claims 1-20 of USSN 10/838,789

A statutory double patenting rejection can be overcome by showing that the claims in question are not the same invention. The "same invention" means identical subject matter.

Claims 1-20 were canceled in the Preliminary Amendment filed on May 3, 2004 and Claims 63-68 were added. Claims 63-68 are directed to a method for the treatment of a functional bowel disorder in a patient suffering therefrom, comprising administering to the patient an effective amount of (4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine or a salt thereof. It is noted that the present rejection is a provisional rejection

under 35 U.S.C. § 101. Applicant notes this rejection and will address this rejection, if appropriate, upon indication that the only remaining rejections are the Double Patenting rejections.

Analysis of Claims 1-20 of USSN 10/841,317

Claims 1-20 were canceled in the Preliminary Amendment filed on May 7, 2004 and Claims 63-70 were added. Claims 63-70 are directed to a pharmaceutical composition in unit dosage form comprising Formula I. In contrast, the claims of the present Application are directed to a method of treating a functional bowel disorder, including diarrhea-predominant irritable bowel syndrome, in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a compound of Formula I and Formula II (MCI-225). The claims of the '317 Application and the claims of the present Application are not directed to the same invention.

Analysis of Claims 1-20 of USSN 10/841,319

Claims 1-20 were canceled in the Preliminary Amendment filed on June 11, 2004 and Claims 63-72 were added. Claims 63-72 are directed to a method for treating a functional bowel disorder comprising administering about 0.001 mg to about 1000 mg per day of a compound of Formula I. In contrast, the claims of the present Application are directed to a method of treating a functional bowel disorder, including diarrhea-predominant irritable bowel syndrome, in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a compound of Formula I and Formula II (MCI-225). The claims of the '319 Application and the claims of the present Application are not directed to the same invention.

Analysis of Claims 1-20 of USSN 10/866,593

Claims 1-20 were canceled in the Preliminary Amendment filed on May 7, 2004 and Claims 63-130 were added. Claims 63-130 are directed to a method of treating pain or discomfort associated with a functional bowel disorder comprising administering from about 0.02 mg to about 200 mg per day or about 0.1 mg to about 50 mg per day of a compound of Formula I and Formula II. In contrast, the claims of the present Application are directed to a

method of treating a functional bowel disorder, including diarrhea-predominant irritable bowel syndrome, in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a compound of Formula I and Formula II (MCI-225). The claims of the '593 Application and the claims of the present Application are not directed to the same invention.

Reconsideration and withdrawal of the rejection are respectfully requested

Rejection of Claims 1-20 under 35 U.S.C. §103(a)

The Examiner rejected Claims 1-20 as being obvious over Greenbaum *et al.*, "Effects of Desipramine on Irritable Bowel Syndrome Compared with Atropine and Placebo," *Digestive Diseases and Sciences, 32*(3): 257-266 (1987) (hereinafter "Greenbaum") in view of Ninomiya *et al.* (U.S. Patent No.4,695,568) (hereinafter "Ninomiya") . In particular, the Examiner stated that Greenbaum teach in general that antidepressants treat IBS, Ninomiya teach compounds of Applicant's Formula I to treat depression and that substitution of Ninomiya's compounds as the antidepressant of Greenbaum carries a reasonable expectation of success in treating IBS. Applicant respectfully disagrees.

Applicant's invention

Applicant's invention is directed to a method of treating a functional bowel disorder, including diarrhea-predominant irritable bowel syndrome, in a subject in need thereof comprising administering to said subject a therapeutically effective amount of a compound of Formula I and Formula II (MCI-225).

Antidepressant Categories Differ Stucturally and Mechanistically

As a preliminary matter, Applicant would like to clarify that there are many different categories of anti-depressants (drugs that treat depression) differing in chemical structure and mechanism of action. Exhibit 1 provides a listing of the various categories of anti-depressants. The categories include:

TCAs;

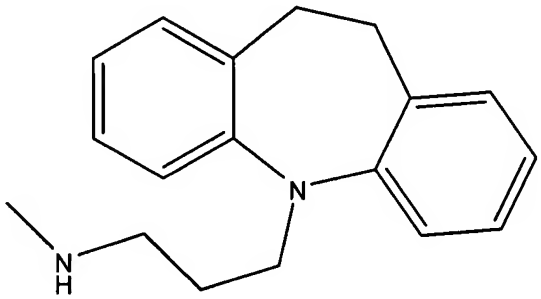
SSRIs (selective serotonin reuptake inhibitors);

MAOIs (monoamine oxidase inhibitors); and

Others, such as venlafaxine, nefazodone, bupropion, and mirtazapine.

TCAs are named after their molecular structure. TCAs contain three rings fused together with the two end rings being phenyl. In addition, the TCAs have either a tertiary or a secondary amine which also contributes to drug activity. Most of the TCAs (e.g., desipramine, trimipramine, nortriptyline and amitriptyline) inhibit the reabsorption of noradrenaline (NA). The structure of despramine is provided below, showing both the three ring structure common to TCAs and presence of an amine functionality.

Desipramine:



SSRIs increase the extracellular level of the neurotransmiiter serotonin by inhibiting the reuptake in to the presynatpic cell, thereby increasing the level of serotonin available to bind to the postsynaptic receptor.

MAOIs on the other hand act by inhibiting the activity of monoamine oxidase, thereby preventing the breakdown of monoamine neurotransmitters, which increases their availability.

Under the Other category, venlafaxine is a serotonin-norepinephrine reuptake inhibitor; nefazodone is a blocker of the post-synaptic serotonin type-2A receptor; bupropion is a norepinephrine and dopamine reuptake inhibitor and nicotinic antagonist; and mirtazapine is a norephinephrine antagonist and serotonin antagonist.

As such, although one anti-depressant, (e.g., the tricyclic antidepressant, desipramine, of Greenbaum) may show some usefulness in treating IBS, one of skill in the art would not expect that antidepressants generally will be useful in treating IBS, because of the diversity in structure and mechanism of action which exists among the various categories of antidepressants.

One of ordinary skill in the art upon reading Greenbaum would have no reasonable expectation of success in treating IBS using all categories of antidepressants, simply because they have antidepressant action. More specifically, Greenbaum discusses that reports of psychotropic agents (e.g., anxiolytics and antidepressants) in the treatment of IBS have been difficult to interpret for a number of reasons, such as an inadequate definition of IBS, lack of

placebo controls and use of drug combinations. Greenbaum further provides a summary of placebo-controlled IBS trials of antidepressants, all of which are tricyclic antidepressants, reporting that some show usefulness (e.g., trimpramine and amitriptyline), others do not and still others show usefulness in some IBS studies and not others. Notably, Greenbaum's summary reports that desipramine, the only antidepressant used in Greenbaum's study, showed usefulness in one reported IBS study, but not another.

In view of the above, one of ordinary skill in the art upon reading Greenbaum would have no reasonable expectation that all categories of antidepressant would be useful in treating IBS simply because they treat depression. In fact, one of ordinary skill in the art would not even be motivated to use the particular category, tricyclic antidepressant (the type of antidepressant used in Greenbaum), with any reasonable expectation of success, because earlier studies reported in Greenbaum using tricyclics did not demonstrate usefulness. It is clear that at best Greenbaum's teachings are limited to use of desipramine and that the prior art, in fact, conflicts with Greenbaum regarding the usefulness of desipramine.

The Compounds of Applicant's Claimed Method Lack Antimuscarinic Activity

Even, assuming arguendo, that one of ordinary skill in the art would be motivated by Greenbaum to use all antidepressants to treat IBS, there would be no reasonable expectation of success in treating IBS with a compound, such as MCI-225, that lacks antimuscarinic activity. Greenbaum teaches that the usefulness of desipramine relies not only on its antidepressant effects, but on its antimuscarinic activity (See, page 264, col. 2 and Abstract). Therefore, one of ordinary skill in the art would not be motivated to use a compound that lacks antimuscarinic activity, such as the compounds used in Applicant's claimed methods (e.g., the MCI-225 of Claims 15 and 20). As such, Greenbaum could be construed as a teaching away of compounds which lack antimuscarinic activity, such as the compounds set forth in Applicant's claimed method (e.g., the MCI-225 of Claims 15 and 20).

Details relating to the pharmacological profile of MCI- 225 are provided in Eguchi *et al.*, "Pharmacological Profile of the Novel Antidepressant 4-(2-Fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno-[2,3d]pyrimidine Monohydrate Hydrochloride," *Arzeneimittel Forschung 47*: 1337-1347 (1997) (hereinafter "Eguchi") (Exhibit 2). Eguchi studied the neuropharmacological

profile of MCI-225 in comparison to various compounds including desipramine. As discussed above, desipramine has both anti-depressant and antimuscarinic activity. MCI-225, however, lacks any significant antimuscarinic activity. For purposes of the following discussion, antimuscarinic activity can be considered the same as anticholinergic activity. More specifically, antimuscarinic agents block the action of acetylcholine on the muscarinic acetylcholine receptor.

Eguchi reports an *in vitro* assay testing the inhibition of radioligand binding by MCI-225 to various rat brain receptors, wherein the binding at the muscarinic receptor resulted in an IC_{50} of 9.1 μmol/l (page 1341 and Table 3), in comparison to nanomolar ranges for other receptors (e.g., 81 nmol/l for 5-HT_3 receptor), thereby demonstrating that binding of MCI-225 to the muscarinic receptor was insignificant. Thus, MCI-225 lacks the antimuscarinic activity upon which Greenbaum relies in reporting the usefulness of desipramine in treating IBS. Consequently, one of ordinary skill in the aret would not be motivated to use a compound having antidepressant activity to treat IBS, particularly if the compound lacks anticholinergic acitivity.

Eguchi further reports that MCI-225 did not inhibit oxotremorine-induced tremor, salivation or lacrimation, supporting the *in vitro* binding assays, suggesting that MCI-225 does not exhibit central and peripheral anticholinergic effects. The lack of anticholinergic action is thought to be due to the low affinity of MCI-225 for the muscarinic receptors and its 5-HT_3 receptor antagonist action (Eguchi, page 1346, col. 1). In addition, Eguchi reports that the weaker suppression of REMS (rapid eye movement sleep) by MCI-225, in comparison to desipramine, may also reflect a lack of an anticholinergic effect from MCI-225 (Eguchi, page 1346, col. 2).

As such, Eguchi teaches that MCI-225 lacks any signigicant anticholinergic effects. As such, one of ordinary skill in the art would not substitute MCI-225 for the desipramine of Greenbaum, because one of the activities of desipramine (anticholinergic activity) upon which Greenbaum relies upon in treating IBS, is not part of the pharmacological profile of MCI-225.

Desipramine and the Compounds of the Claimed Method are Pharmacologically Distinct

Moreover, the desipramine used by Greenbaum and the compounds of Applicant's claimed methods (e.g., MCI-225) have distinct pharmacological properties which go beyond the lack of antimuscarinic activity. For example, Eguchi reports that even though MCI-225 has

noradrenaline (NA) reuptake inhibitor acitivty, the NA reuptake inhibition of MCI-225 is much less potent than desipramine; and MCI-225 has 5-HT_3 receptor antagonist activity, but desipramine does not. Therefore, one of ordinary skill in the art would not substitute the compounds of Applicant's claimed method for the desipramine of Greenbaum or even for tricyclics as a whole, with any reasonable expectation of success, because they are pharmacologically distinct. In other words, substitution of Applicant's compounds for desipramine or a tricyclic antidepressant is not a simple substitution which would provide predictable results. These distinctions are discussed in detail below.

MCI-225 is a 5-HT_3 receptor antagonist, desipramine is not. In an *in vitro* radioligand binding assay testing the ability of MCI-225 and desipramine to inhibit the binding of ^{3}H-GR65630 for the 5-HT_3 receptor in N1E-115 cells, it was found that MCI-225 inhibited binding with a K_i value of 3.04 nmol/l, whereas desipramine had a K_i value of 1098 nmol/l. (Eguchi, page 1341 and Fig. 2). This data demonstrates that MCI-225 is a 5-HT_3 receptor antagonist, whereas desipramine is not. The 5-HT_3 receptor antagonist activity of MCI-225 is thought to be a unique pharmacologic profile compared to desipramine (page 1345, col. 2). Further, it is noted that 5-HT_3 receptor antagonists are reported to enhance acetylcholine release (FIG. 7 and page 1345, col. 2), which follows with the above discussion that MCI-225 lacks any significant antimuscarinic/anticholinergic activity, which Greenbaum relies on for usefulness in treating IBS.

Desipramine is a more potent noradrenaline uptake inhibitor than MCI-225. In an *in vitro* radioligand binding assay testing the ability of MCI-225 and desipramine to inhibit synaptosomal uptake of noradrenaline (NA) in rat brain synaptosomes, it was found that MCI-225 did not inhibit the uptake of NA as potently as desipramine. (Eguchi, page 1340, col. 2 and Fig. 1). Thus, desipramine is a more potent noradrenaline uptake inhibitor than MCI-225 and one of ordinary skill in the art would not be motivated to select a less potent substitute.

Thus, one of ordinary skill in the art, upon reading Greenbaum, would not be motivated to substitute MCI-225 for desipramine with any reasonable expectation of success. In other words, MCI-225 is not a simple substitute for the desipramine of Greenbaum or for tricyclic antidepressants in general.

The teachings of Ninomiya do not cure the deficiencies of Greenbaum. Ninomiya teaches that 4-(2-fluorophenyl)-6-methyl-2-piperazinyl-thieno[2,3-d]pyrimidine (MCI-225) is potentially useful for the treatment of depression. Ninomiya does not teach or suggest that MCI-225 may be useful in treating IBS. Eguchi provides additional details of the pharmacological profile of MCI-225 which distinguish it from tricyclic antidepressants, such as desipramine. As such, one of ordinary skill in the art would not be motivated to substitute MCI-225 for the tricyclic antidepressant desipramine of Greenbaum with any reasonable expectation of treating IBS.

Thus, none of the references alone or in combination teach or suggest the claimed invention. Applicant's claimed invention is non-obvious. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-20 under 35 U.S.C. §103(a)

The Examiner rejected Claims 1-10, 12 and 14-20 as being unpatentable over Bardsley *et al.*, (WO 02/094249 A1) (hereinafter "Bardsley") in view of Sanger *et al.* (WO 94/01095) (hereinafter "Sanger").

In particular, the Examiner stated that Bardsley teaches the use of 4-(2-fluorophenyl)-6-methyl-2-piperazinyl-thieno[2,3-d]pyrimidine for treating pain, but fails to teach the nexus between pain and IBS. The Examiner then relies on Sanger for its teaching that pain is a symptom of IBS thereby providing the necessary nexus. Applicant respectfully disagrees, because one of ordinary skill in the art would not expect that MCI-225 would be as effective in treating the visceral pain of IBS based on Bardsley's demonstration of treating inflammatory pain. In other words, the model of inflammatory pain is not predictive of similar efficacy of MCI-225 in other types of pain, because the different types of pain (i.e., nociceptive, inflammatory and neuropathic) are associated with differing underlying mechanisms, etiologies and pathophysiologies and are treated with drugs specific for the type of pain. These conclusions are discussed in detail below.

Bardsley would not motivate one of ordinary skill in the art to treat the visceral pain associated with IBS using MCI-225. More specifically, Bardsley generally discusses the use of 4-(2-fluorophenyl)-6-methyl-2-(1-piperazinyl)thieno[2,3-D]pyrimidine, which is referred to in

the application as MCI-225, for the treatment of pain. However, Bardsley only demonstrates the treatment of inflammatory pain.

Types of Pain:

There are three types of pain: nociceptive, inflammatory and neuropathic pain.

Nociceptive pain (See Exhibit 4, Paragraph 8.2, Subheading "Nociceptive pain.")

Nociceptive pain refers to the pain sensation evoked by activation of nociceptors located in non-damaged skin, viscera and other organs in the absence of sensitisation (e.g., in the absence of clinically relevant inflammation, tissue damage or other pathology). Nociceptive pain arising from the visceral organs (e.g., gastrointestinal tract, kidneys, gallbladder, bladder) is called visceral pain, while pain arising from the skin, muscle, joint capsules and bone is called somatic pain. Somatic pain is often highly localised to a specific area, however visceral pain is generally poorly localized. An example of nociceptive pain arising form the visceral organs is the abdominal pain associated with Irritable Bowel Syndrome. A diagnosis of IBS presumes the absence of a structure of biochemical explanation for the symptoms.

Inflammatory pain (See Exhibit 4, Paragraph 8.2, Subheading "Inflammatory pain.")

Inflammatory pain refers to pain sensation that arises in inflamed tissue following sensitisation of peripheral pain receptors. Examples of inflammatory pain include the pain associated with the inflammation of arthritis and other body tissues, for example tendinitis and bursitis. Such pain is usually treated with peripherally acting non-steroidal anti-inflammatory drugs, or NSAIDs, which reduce inflammation. Inflammatory pain is the type of pain exemplified by Bardsley at pages 3 to 4. The distinction between nocipetive and inflammatory pain is reviewed by Woolf, CJ and Costigan, M. "Transcriptional; and Posttranslational Plasticity and the Generation of Inflammatory Pain," *PNAS, 96*: 7723-7730 (1999) (Exhibit 3).

Neuropathic pain (See Exhibit 4, Paragraph 8.2, Subheading "Neuropathic pain.")

Neuropathic pain refers to pain sensation that develops secondary to a dysfunction of, or damage to, a nerve or group of nerves particularly peripheral nerves, although pain due to CNS damage ("central pain") may share these characteristics. Neuropathic pain is treated with tricyclic anti-depressants.

For a more detailed discussion on the types of pain and Bardsley's exemplification of inflammatory pain, please see Exhibits 4-6, which are copies of Declarations by Maree Therese

Smith (Exhibits 4 and 5) and Colin Stanley Goodchild (Exhibit 6), which were filed in Opposition Proceeding in the Australian counterpart application to Bardsley (AU Application No.: 2004204825).

One of ordinary skill in the art would not expect that MCI-225 would be as effective in treating the visceral pain of IBS based on Bardsley's demonstration of treating inflammatory pain. Bardsley's experimental section (pages 3-4) describes the use of MCI-225 in an *in vivo* model of inflammatory pain only. The model of inflammatory pain is not predictive of similar efficacy of MCI-225 in other types of pain, because as discussed above, the different types of pain are associated with differing underlying mechanisms, etiologies and pathophysiologies and are treated with drugs specific for the type of pain. Inflammatory pain is generally treated with peripherally acting non-steroidal anti-inflammatory drugs, or NSAIDs which reduce inflammation (See Exhibit 4, Paragraph 8.2, subheading "Inflammatory pain."). On the other hand, nociceptive pain, such as the visceral pain of IBS, is generally treated with drugs which effect the sensory and motor function of the gut (See Exhibit 4, Paragraph 8.2, subheading "Nociceptive pain."). Accordingly, efficacy of an agent in the treatment of one type of pain is not a predictor of efficacy in the treatment of other types of pain.

Moreover, Bardsley at page 1 lines 16-26 supports the conclusion that the efficacy of an agent in the treatment of one form of pain is not a predictor of similar efficacy in the treatment of other forms of pain. For example, Bardsley teaches that although inflammatory pain can be managed with NSAIDs, COX-2 inhibitors, tramadol and opiates, there are few adequate treatments that exist for neuropathic pain. Therefore, the description of the use of MCI-225 in an *in vivo* model of inflammatory pain (see pages 3 to 4 of Bardsley), is not pertinent to or predictive of efficacy of MCI-225 in neuropathic pain. Similarly, efficacy of an agent (e.g., an NSAID such as indomethacin), in the treatment of inflammatory pain is not a predictor of efficacy in the treatment of non-inflammatory pain, such as the pain associated with IBS.

Simply put, the visceral pain of IBS is not caused by inflammation. Bardsley has demonstrated treatment of pain caused by inflammation using MCI-225. Based on this demonstration by Bardsley, one of ordinary skill in the art would not expect similar efficacy in treating a type of pain <u>not associated with inflammation</u> (e.g., the visceral pain of IBS).

Therefore, one of ordinary skill in the art would not recognize the model of inflammatory

pain described in Bardsley as predictive of drug efficacy in the treatment of non-inflammatory pain and would not expect similar efficacy in treating non-inflammatory pain, such as the visceral pain associated with IBS, using MCI-225.

The teachings of Sanger do no cure the deficiencies of Bardsley. Sanger teaches the use of 5-HT_3 receptor antagonists for the treatment of visceral pain, such as the pain symptoms of IBS. Sanger does not teach or suggest MCI-225 and Bardsley would not motivate one of ordinary skill in the art to substitute MCI-225 for the agents of Sanger.

Thus, none of the references alone or in combination teach or suggest the claimed invention. Applicant's claimed invention is non-obvious. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

HAMILTON, BROOK, SMITH & REYNOLDS, P.C.

By Susan M. Abelleira

Susan M. Abelleira
Registration No. 42,252
Telephone: (978) 341-0036
Facsimile: (978) 341-0136

Concord, MA 01742-9133

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